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The Relationship of Lid Wiper Epitheliopathy to Ocular Surface Signs and Symptoms

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PURPOSE. There has been interest in determining whether lid wiper epitheliopathy (LWE) plays a key role in causing ocular discomfort. Conflicting reports have made it difficult to discern whether LWE is more prevalent in certain populations, what characteristics are associated with its severity, and what its role is in symptomatology. This cross-sectional study on a large and diverse population attempts to answer these questions.

METHODS. Subjects were asked to complete questionnaires related to dry eye and to ocular discomfort. A comprehensive set of ocular surface parameters were assessed, including LWE length and width, tear-film lipid layer thickness, fluorescein tear breakup time (FTBUT), lid-parallel conjunctival folds (LIPCOF), and corneal staining.

RESULTS. A total of 287 subjects participated in the study. LWE was observed in 45% of the study cohort and was twice as prevalent in Asians than non-Asians ($P < 0.005$). LWE was more likely to present in contact lens wearers than non-contact lens wearers ($P = 0.03$). Decreased FTBUT was associated with increased LWE length and width ($P < 0.005$ and $P = 0.01$, respectively), although only a small effect size was noted. Presence of LIPCOF was linked with a 0.25-grade increase in LWE width ($P = 0.01$). Only LWE width was associated with greater symptoms in contact lens wearers.

CONCLUSIONS. LWE was associated with decreased tear-film stability, contact lens wear, lid anatomy, and LIPCOF. LWE was not associated with symptoms in non-contact lens wearers. LWE width was associated with greater symptoms in contact lens wearers but was only clinically significant with moderate to severe LWE width.

Keywords: lid wiper epitheliopathy, dry eye, ocular surface, soft contact lens, ethnicity

The importance of the tear film in providing optical clarity and protection to the eye has led to interest in determining what area of the eyelid is responsible for spreading tear film during the blink cycle. Histologic examination of the eyelid by Knop et al.¹ has identified a region of stratified squamous epithelium on the marginal palpebral conjunctiva, referred as the lid wiper, that based on the cell type was suggested to come in contact with the exposed anterior ocular surface. Shaw et al.² have found additional evidence for this when they placed pressure-sensitive paper between the eye and the upper eyelid, and have found that the area outlined closely matches the estimated dimension of the lid wiper.

The identification of the lid wiper has led to interest in determining whether its disruption by increased shear stress during blinks, termed the "lid wiper epitheliopathy" (LWE), contributes to dry eye and contact lens discomfort.³⁻⁵ The etiology of LWE is hypothesized to be due to shear stress to the lid wiper. The tribological model for LWE formation, proposed by Pult et al.,⁶ is based on the concept that shear stress generated during blinks is reduced by the presence of the tear film and mucins. Under this model, the tear film minimizes friction during blinks by acting as a low-viscosity lubricant to maximize the time that blinks stay in the hydrodynamic regime, and can only occur as long as the tear film is sufficiently thick to mask irregularities on the ocular surface.⁶ This led to the hypothesis that tear film instability could contribute to LWE

formation,³⁻⁵ as it is thought that a region of instability represents an area of increased tear film evaporation.^{7,8} Greater tear film evaporation potentially increases friction because it is associated with significant thinning of the tear film, which could prevent masking of ocular surface irregularities, and because of increased osmolarity,⁸ which can inhibit mucin production.⁹ LWE formation has also been attributed to lid pressure, tear composition, tear viscosity, surface texture, and blink velocity.^{3-5,10} As contact lens wear is associated with increased tear film instability,¹¹ it may explain why LWE may occur more frequently among contact lens wearers, possibly more so in contact lenses with a higher coefficient of friction.^{10,12} It has been hypothesized that the subsequent irregularities in the lid wiper region can lead to greater friction during blinks, which translates to a corresponding increase in ocular discomfort and dryness.^{3-5,13}

Several groups^{3-5,12,14,15} have found evidence to support these findings and have additionally argued that LWE may be the missing key in explaining the discrepancy often noted between signs and symptoms related to dry eye and contact lens discomfort. Interestingly, other groups¹⁶⁻¹⁸ have failed to find corroborating evidence. These conflicting results have made it difficult to discern whether LWE is a true pathology or an acceptable physiological variation of the lid wiper.¹³ In addition, there have also been questions regarding whether certain demographic groups are more likely to present with



LWE.^{13,18} Therefore, the purpose of this study was to gain greater clarity about the clinical significance of LWE through a cross-sectional study on a large and diverse population, using a comprehensive set of ocular surface assessments. There were three aims in this study: (1) to compare LWE prevalence rates among demographic groups, (2) to determine if subject characteristics or ocular surface features were associated with severity of LWE, (3) and to assess if LWE was associated with patient symptomology.

METHODS

Study Population

Subjects were recruited for this one-visit study from the University of California, Berkeley, and the surrounding community. Subjects were excluded if they would not discontinue contact lens wear, makeup, artificial tears, or facial lotion use for at least 24 hours before their visit. A 24-hour washout for contact lens wear was needed to minimize any potential confounding effects from exposure to contact lens and/or contact lens solution.¹¹ They were also excluded if they presented with active ocular infection or inflammation. Both contact lens wearers and non-contact lens wearers were recruited for this study. Subjects were defined as non-contact lens wearers if they had never worn contact lenses or had discontinued contact lens wear more than 1 year before study participation. Among contact lens wearers, only those who wore soft contact lenses were included in the analysis. Individuals were considered to be Asian if they were of Chinese, Taiwanese, Japanese, Vietnamese, or Korean descent, or a mixture of these ethnicities. Individuals were considered to be non-Asian if they were of any other ethnicity (e.g., European Caucasian, Latin American, African, or Spanish descent, or a mixture thereof). Though ocular anatomy is different between ethnicities in the non-Asian group (e.g., African versus European Caucasian), the decision to compare Asian and non-Asian was based on studies that have examined these two groups and found marked differences in dry eye prevalence rates, as well as in ocular anatomy and physiology.^{19–21} Written informed consent, with a complete description of the goals, risks, benefits, and procedures of the study, was obtained from all participants. This study observed the tenets of the Declaration of Helsinki and was approved by the University of California, Berkeley Committee for Protection of Human Subjects.

Study Protocol

Subjects were administered a battery of questionnaires composed of the Ocular Surface Disease Index (OSDI), Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire, Dry Eye Flow Chart (DEFC), and a set of 100-point visual analog rating scales for (1) average and end-of-day comfort (0 = “poor comfort, intolerable,” 100 = “excellent comfort”); (2) frequency of discomfort on average and at end-of-day (0 = “never,” 100 = “all the time”); (3) average and end-of-day dryness (0 = “no sensation of dryness whatsoever,” 100 = “extremely dry, intolerable”), and (4) frequency of dryness on average and at end-of-day (0 = “never,” 100 = “all the time”). Contact lens wearers were also asked to complete the Contact Lens Dry Eye Questionnaire-8 (CL-DEQ 8). These dry eye and ocular discomfort questionnaires were chosen because they are the common questionnaires used clinically and each questionnaire likely provides insights on different dimensions of symptomology.^{22–26} Investigators were masked to the results of these questionnaires. In addition, a demographics and

history questionnaire was administered that included items for age, sex, ethnicity, and contact lens wear history (years of wear, average daily hours of wear, average daily hours of comfortable wear, and days per week of wear). The questionnaire packet took approximately 30 minutes to complete and the order of the questionnaires was randomized to minimize any potential bias due to the effects of test fatigue.

A comprehensive set of anterior ocular health tests was performed for both eyes, with the test order selected from least to most invasive procedure. Subjects were initially taken to an exam room where tear-film lipid layer thickness was measured with the LipiView interferometer (TearScience, Inc., Morrisville, NC, USA). Tear meniscus height was then assessed with the Oculus Keratograph 5M (Oculus, Inc., Arlington, WA, USA). Noninvasive tear breakup test (NITBUT) was done three times for each eye (with the mean value used for analysis) by using the Medmont E300 corneal topographer (Medmont International Pty Ltd, Victoria, Australia), alternating between eyes, with a 30-second break between each measurement, and an endpoint consisting of the first visible disruption noted on the Placido mires; NITBUT was repeated if a subject blinked before disruption was observed.

Subjects were then taken to another exam room where a white light slit lamp (SL120; Carl Zeiss Meditec, Inc., Jena, Germany) examination was conducted for blepharitis²⁷ and for limbal and bulbar redness²⁸; the grading criteria used for these and other ocular surface assessments used in this study are described in more detail in Table 1. An examination at $\times 20$ magnification was made in the lower nasal or temporal conjunctiva for lid-parallel conjunctival folds (LIPCOF); LIPCOF were not assessed with a grading scale, but rather whether they were present or not.¹⁴ One microliter of 2% sodium fluorescein was then applied to each eye by using a 1- to 10- μ L adjustable-volume micropipette (Eppendorf, Hamburg, Germany).²⁹ Shortly after sodium fluorescein instillation, fluorescein tear breakup time (FTBUT) was measured three times for each eye (with the mean value used for analysis), alternating between eyes, and with a 30-second break between each measurement. FTBUT measurement was done approximately 10 to 15 minutes after NITBUT, and enough time should have elapsed for the tear film to recover. The inclusion of both NITBUT and FTBUT was based on a recent study by Yeh et al.,³⁰ which suggests that these two tests may be assessing different aspects of tear film breakup. Corneal staining type, depth, and extent were evaluated by using the CCLRU grading scale.²⁸ FTBUT and corneal staining were assessed under cobalt blue illumination and viewed through a 530-nm yellow barrier filter. Before meibum expression was done, investigators gently blotted a cotton applicator along the upper and lower eyelid margin to remove any fluid or debris that could potentially block expression. The Korb Meibomian Gland Evaluator (TearScience, Inc., Morrisville, NC, USA) was used to apply a force of approximately 1.25 g/mm² at a 45° angle against the superior and inferior eyelid (individually assessing the nasal, central, and temporal regions) for 10 to 12 seconds. Every gland observed to be expressible was assessed for quality and quantity of meibum secretion.^{31,32}

One drop of 1% Lissamine Green (Leiter's Compounding Pharmacy, San Jose, CA, USA) was applied, and conjunctival staining was graded by using the SICCA grading scale,³³ with Line of Marx also assessed.³⁴ Five minutes following the initial instillation of Lissamine Green, a second drop was applied, and after waiting another minute, lid wiper epitheliopathy length and width were evaluated on the upper lid only.^{4,5} Infrared meibography was then conducted on the upper and lower eyelid with the Oculus Keratograph 5M, where gland count and the level of meibomian gland atrophy was gauged.³⁵ Palpebral redness on the upper lid was then examined with a

TABLE 1. Grading Criteria for Ocular Surface Assessments Used in Study

Assessment	Author	Grading Criteria
Blepharitis	Brubaker et al. ²⁷	0: Clear eyelid margin 1: Occasional fragment (scurf), 1 to 5 collarettes 2: Few fragments, 6 to 20 collarettes 3: Many fragments, 21 to 40 collarettes 4: Clumps/strands, >40 collarettes
Limbal and bulbar redness	Terry et al. ²⁸ (CCLRU Grading Scale)	0: Absent 1: Very slight 2: Slight 3: Moderate 4: Severe
LIPCOF	n/a	0: Absent 1: Present
Corneal staining type	Terry et al. ²⁸ (CCLRU Grading Scale)	0: Absent 1: Micropunctate 2: Macropunctate 3: Coalescent macropunctate 4: Patch
Corneal staining extent	Terry et al. ²⁸ (CCLRU Grading Scale)	0: Absent 1: 1% to 15% surface involvement 2: 16% to 30% surface involvement 3: 31% to 45% surface involvement 4: >46% surface involvement
Corneal staining depth	Terry et al. ²⁸ (CCLRU Grading Scale)	0: Absent 1: Superficial epithelial involvement 2: Stromal glow present within 30 s 3: Immediate localized stromal glow 4: Immediate diffuse stromal glow
Meibomian gland expression quality	Greiner ³¹ and Satjawatcharaphong et al. ³²	0: No secretion 1: Inspissated/toothpaste 2: Cloudy liquid secretion 3: Clear liquid secretion
Meibomian gland expression quantity	Greiner ³¹ and Satjawatcharaphong et al. ³²	0: No secretion 1: Minimal volume 2: Moderate volume 3: Copious volume
Conjunctival staining	Whitcher et al. ³³ (SICCA Grading Scale)	0: 0 to 9 dots 1: 10 to 32 dots 2: 33 to 100 dots 3: >100 dots
LOM	Yamaguchi et al. ³⁴	0: All of LOM posterior to meibomian glands 1: Parts of LOM touching meibomian glands 2: LOM running along meibomian glands 3: All of LOM anterior to meibomian glands
Lid wiper epitheliopathy length	Korb et al. ^{4,5}	0: <2 mm 1: 2 to 4 mm 2: 5 to 9 mm 3: ≥10 mm
Lid wiper epitheliopathy width	Korb et al. ^{4,5}	0: <25% of the width of wiper 1: 25% to <50% of the width of wiper 2: 50% to <75% of the width of wiper 3: ≥75% of the width of wiper
Meibomian gland atrophy	Arita et al. ³⁵	0: 0% of total meibomian gland area affected 1: <33% of total meibomian gland area affected 2: 33% to 66% of total meibomian gland area affected 3: >67% of total meibomian gland area affected
Palpebral redness	Terry et al. ²⁸ (CCLRU Grading Scale)	0: Absent 1: Very slight 2: Slight 3: Moderate 4: Severe
Lagophthalmos	Blackie & Korb ³⁶	0: Absent 1: Present

LOM, Line of Marx; n/a, not applicable.

TABLE 2. Mean, Standard Deviation, and Range for Measurements in All Subjects

	Mean (SD)	Range
Age, y	28.0 (13.3)	18–71
OSDI score	13.1 (13.6)	0.0–70.8
SPEED 2 score	6.3 (4.9)	0.0–22.0
DEFC score	2.5 (1.5)	1.0–5.0
Average comfort, visual analog scale	77.5 (21.5)	3.0–100.0
End-of-day comfort, visual analog scale	22.2 (22.7)	0.0–99.0
Frequency of average discomfort, visual analog scale	69.5 (27.3)	0.0–100.0
Frequency of end-of-day discomfort, visual analog scale	28.5 (27.7)	0.0–100.0
Average dryness, visual analog scale	25.7 (25.0)	0.0–100.0
End-of-day dryness, visual analog scale	23.5 (24.4)	0.0–100.0
Frequency of average dryness, visual analog scale	28.9 (28.1)	0.0–100.0
Frequency of end-of-day dryness, visual analog scale	28.5 (28.7)	0.0–100.0
Average tear-film lipid layer thickness, nm	63 (20)	21–100
Blepharitis	1.2 (1.4)	0.0–6.0
Bulbar redness	3.0 (2.0)	0.0–11.0
Corneal staining type	0.9 (1.4)	0.0–10.0
Corneal staining extent	0.7 (1.2)	0.0–14.0
Corneal staining depth	0.8 (1.0)	0.0–6.0
Conjunctival staining	1.6 (2.0)	0.0–12.0
Fluorescein tear breakup time, s	8.2 (8.4)	0.5–60.3
Lid wiper epitheliopathy length	0.8 (1.1)	0.0–3.0
Lid wiper epitheliopathy width	0.6 (0.9)	0.0–3.0
Limbal redness	2.0 (2.1)	0.0–11.0
Line of Marx	1.5 (1.3)	0.0–6.0
Meibography atrophy score	1.3 (1.4)	0.0–6.0
Meibography gland count	34.2 (6.7)	16.0–56.0
Meibomian gland expression quality score	39.5 (26.5)	0.0–145.0
Meibomian gland expression quantity score	28.7 (20.9)	0.0–112.0
Noninvasive tear breakup time, s	12.0 (12.1)	1.6–110.0
Palpebral redness	1.1 (0.6)	0.0–2.5
Schirmer strip, mm	17.6 (10.0)	0.0–35.0
Tear meniscus height, mm	0.25 (0.09)	0.09–0.51

slit lamp.²⁸ Presence or absence of lagophthalmos was observed with the transilluminator technique described by Blackie et al.³⁶ In the final test, tear production was measured by using Schirmer's Strip Test 1 (without anesthetic). Room temperature and humidity were measured by using a combination digital thermometer and hygrometer (General Tools & Instruments, Secaucus, NJ, USA). Mean room temperature and humidity were $23^{\circ}\text{C} \pm 1^{\circ}\text{C}$ and $50\% \pm 8\%$, respectively.

Statistical Methods

Data were analyzed with R statistical package (version 3.3.2; R foundation for Statistical Computing, Vienna, Austria). In all statistical models, results with $P \leq 0.05$ and $P \leq 0.10$ were considered statistically significant and borderline significant, respectively. There were three goals of the analysis: (1) compare prevalence rates of LWE between different demographic groups, (2) assess if certain subject characteristics and ocular surface measurements were associated with grade of LWE, and (3) determine if LWE grade was correlated to patient symptomatology. For the first goal, subjects were categorized and prevalence was calculated on the basis of sex, contact lens wear status, ethnicity (Asians versus non-Asians), and age (those ≤ 30 years versus those ≥ 50 years). The decision to categorize age by using this criterion was based on work by Vihlen and Wilson,³⁷ which has found that lid tension declines at approximately 50 years of age. The prevalence rate of LWE was defined as a subject having \geq grade-1 LWE length or LWE width in at least one eye. Afterwards, comparison of two

proportions testing using Z-test was conducted to determine if LWE prevalence rates between demographic groups were significantly different. Comparisons in the composition of demographic groups were assessed by using Student's *t*-test.

To address the second and third goal, a thorough exploratory and descriptive preliminary analysis was conducted by assessing bivariate plots and univariate models by using the ggplot2 R package³⁸ to examine for possible significant associations between explanatory and outcome variables, which guided how multivariate modeling was used. Pearson correlation was examined to ensure there were no issues with collinearity during multivariate modeling. Owing to the variability in interobserver reliability noted in dry eye assessment, investigators were coded as separate categorical variables and factored in all statistical models to account for interobserver variability.³⁹ Aggregate values (i.e., summation of values from all grading zones) for bulbar and limbal redness, conjunctival staining, and corneal staining type, extent, and depth were used for analysis. In addition, aggregate values

TABLE 3. Grade Distribution in Lid Wiper Epitheliopathy Length and Width for the Study Cohort

	Lid Wiper Epitheliopathy Length	Lid Wiper Epitheliopathy Width
Grade 0	63% (362 eyes)	67% (386 eyes)
Grade 1	11% (65 eyes)	15% (85 eyes)
Grade 2	13% (74 eyes)	11% (64 eyes)
Grade 3	13% (73 eyes)	7% (39 eyes)

TABLE 4. Prevalence Rate of LWE for Different Demographics (Sex, Ethnicity, Contact Lens Wearing Status, and Age), With *P* Values Provided From Comparison of Two Proportion Testing*

Subgroup	LWE Prevalence	<i>P</i> Value
Female (<i>n</i> = 194)	45%	0.87
Male (<i>n</i> = 93)	46%	
Non-Asian (<i>n</i> = 160)	33%	<0.005
Asian (<i>n</i> = 127)	61%	
Non-contact lens wearers (<i>n</i> = 148)	39%	0.03
Contact lens wearers (<i>n</i> = 139)	52%	
≤30 years old (<i>n</i> = 224)	46%	0.08
≥50 years old (<i>n</i> = 33)	30%	

Bolded values indicate statistical significance, $P \leq 0.05$.

* Prevalence was defined as a subject having ≥grade-1 LWE length or width in at least one eye.

from the upper and lower lids for blepharitis, Line of Marx, meibum quality and quantity, and meibomian gland count and atrophy score were used. The use of these aggregate values in statistical modeling was decided a priori to minimize the possibility of type 1 error and because our previous studies have found none-to-minimal benefits in sectoral analysis.^{21,40–42} In addition to conducting the analysis using the mean of LWE length and width to generate one value when assessing LWE, we also opted to examine LWE length and width separately because of studies that have found that greater LWE width is associated with symptoms.^{4,5,43,44} Linear mixed effects models using the nlme R package⁴⁵ were used to account for potential within-subject correlations related to measurements done on the right and left eye. The use of the right and left eye in the statistical analysis was designed to account for the intereye variability in ocular surface parameters, and in symptoms of ocular discomfort and dryness for each subject.¹⁸ Upon examining residual plots, FTBUT and NITBUT were natural-log transformed to better approximate normality to meet key assumptions for univariate and multivariate modeling. For multivariate analysis, a stepwise regression procedure with consideration of *F* test *P* values and examination of residual and other diagnostic plots was used to determine accurate models. Interaction terms based on the final set of significant explanatory variables chosen in each multivariate model were considered, using the jtools R package,⁴⁶ but none were found to be significant.

For the second goal, statistical models factored LWE length and width as separate outcome variables, with subject characteristics and ocular surface measurements as potential explanatory variables. Univariate linear mixed effects modeling identified exploratory variables that were associated with LWE length or width. Significant or borderline significant exploratory variables identified in univariate modeling were then examined by using multivariate linear mixed effects modeling.

For the third goal, statistical models factored responses from questionnaires and contact lens wear history (if they were contact lens wearers) as the outcome variable, with LWE length and width as potential explanatory variables. Univariate linear mixed effects modeling identified questionnaires that were associated with LWE length or width. If a significant

association was noted in the univariate model, multivariate linear mixed effects modeling was performed so that other test measurements could be included as potential explanatory variables. This was to ensure that LWE was independently associated with symptoms. This set of analyses was conducted on contact lens wearers and non-contact lens wearers separately, owing to the disparity in how these two groups respond to questionnaires.^{47,48}

As noted in Supplementary Tables S1 through S3, mean LWE value did not provide any additional insights and showed weaker statistical association than when LWE length and width were modeled individually. Therefore, the results will only focus on the LWE length and width as separate variables in the models.

RESULTS

Subject Characteristics

Two hundred eighty-seven subjects completed the study (194 females, 93 males), providing 574 eyes for analysis. The study cohort had a mean (SD) age of 28 (13) years with a range of 18 to 71 years. In the study cohort, there were 127 subjects of Asian descent and 160 subjects of non-Asian descent, and there were 139 soft contact lens wearers and 148 non-contact lens wearers. On average, contact lens wearers in the study wore their contact lenses for 5 days a week and 11 hours a day, with 9 of those hours considered comfortable. Table 2 shows the measurements from all subjects in the study, and Supplementary Tables S4 through S7 examine the demographic composition assessed. When comparing by sex (Supplementary Table S4), men were older (30 years old versus 27 years old; $P = 0.01$) and less likely to wear contact lenses (32% vs. 55%; $P < 0.005$) than women. When comparing by age (Supplementary Table S5), subjects who were ≤30 years old were more likely to be Asian (48% vs. 18%; $P < 0.005$) and contact lens wearers (50% vs. 24%; $P < 0.005$) than subjects who were ≥50 years old. When comparing by ethnicity (Supplementary Table S6), Asians were younger (25 years old versus 31 years old; $P < 0.005$) and more likely to wear contact lenses (61% vs. 33%; $P < 0.005$) than non-Asians. When comparing by contact lens wear status (Supplementary Table S7), contact lens wearers were younger (26 years old versus 30 years old; $P = 0.049$), more likely to be Asian (56% vs. 33%; $P < 0.005$) and female (77% vs. 59%; $P < 0.005$) than non-contact lens wearers.

Prevalence of Lid Wiper Epitheliopathy

Table 3 shows the grade distribution of LWE length and width in the study cohort. Table 4 shows the prevalence of LWE examined based on sex, ethnicity, contact lens wearing status, and age. There were no sex differences in prevalence rates for LWE (females: 45% versus males: 46%; $P = 0.87$). Asians had nearly double the prevalence rate in LWE (61% vs. 33%; $P < 0.005$) as compared to non-Asians. Contact lens wearers had a higher prevalence rate in LWE (52% vs. 39%; $P = 0.03$) as compared to non-contact lens wearers. Younger subjects (≤30

TABLE 5. Final Multivariate Model Showing the Association Between Grade of LWE Length and Significant Explanatory Variables, With Coefficients From the Model Also Listed*

Outcome	Intercept	Ethnicity	Sex	Ln(FTBUT)
Grade of LWE length	1.04	−0.6 ($P < 0.005$)	0.25 ($P = 0.01$)	−0.16 ($P < 0.005$)

Bolded values indicate statistical significance, $P < 0.05$.

* The arbitrary reference groups for ethnicity and sex were Asian and female, respectively.

TABLE 6. Final Multivariate Model Showing the Association Between Grade of LWE Width and Significant Explanatory Variables, With Coefficients From the Model Also Listed*

Outcome	Intercept	Ethnicity	Sex	Ln(FTBUT)	LIPCOF
Grade of LWE width	0.7	−0.50 (<i>P</i> < 0.005)	0.25 (<i>P</i> < 0.005)	−0.12 (<i>P</i> = 0.01)	0.25 (<i>P</i> = 0.01)

Bolded values indicate statistical significance, $P \leq 0.05$.

* The arbitrary reference groups for ethnicity and sex were Asian and female, respectively.

years) had a borderline higher prevalence in LWE length (46% vs. 30%; $P = 0.08$) than older subjects (≥ 50 years).

Factors That Influence Severity of Lid Wiper Epitheliopathy Length

In separate univariate models (Supplementary Table S8), a higher grade of LWE length was associated with being Asian ($P < 0.005$), decreased FTBUT ($P < 0.005$), decreased NITBUT ($P < 0.005$), greater number of meibomian glands ($P = 0.008$), presence of LIPCOF ($P = 0.03$), decreased blepharitis ($P = 0.01$), increased conjunctival staining ($P = 0.02$), and being a contact lens wearer ($P = 0.03$); it was borderline associated with increased bulbar redness ($P = 0.06$), decreased meibomian gland atrophy ($P = 0.07$), and being male ($P = 0.08$). No significant associations were noted with the other parameters. For contact lens wearers, years of contact lens wear were not associated with grade of LWE length ($P = 0.60$).

In multivariate modeling (Table 5), a higher grade of LWE length was associated with decreased FTBUT ($P < 0.005$), being male ($P = 0.01$), and being Asian ($P < 0.005$). Based on the model, an eye with the shortest FTBUT (0.5 seconds) would have an estimated 0.8-grade increase in LWE length, compared to the longest FTBUT (60.3 seconds). Asians had an estimated 0.6 greater grade of LWE length than non-Asians; males had an estimated 0.25 greater grade than females.

Factors That Influence Severity of Lid Wiper Epitheliopathy Width

In separate univariate models (Supplementary Table S9), a higher grade of LWE width was associated with being Asian ($P < 0.005$), decreased FTBUT ($P < 0.005$), decreased NITBUT ($P = 0.01$), greater number of meibomian glands ($P = 0.04$), presence of LIPCOF ($P < 0.005$), increased conjunctival staining ($P = 0.04$), increased bulbar redness ($P < 0.005$), being male ($P = 0.02$), and increased limbal redness ($P < 0.005$). A borderline significant relationship was noted with increased aggregate corneal staining type ($P = 0.08$) and depth ($P = 0.9$), and with increased palpebral redness ($P = 0.08$). No associations were noted with the other parameters. For contact lens wearers, years of contact lens wear were not associated with grade of LWE width ($P = 0.14$).

In multivariate modeling (Table 6), a higher grade of LWE width was associated with decreased FTBUT ($P = 0.01$), being male ($P < 0.005$), being Asian ($P < 0.005$), and the presence of LIPCOF ($P = 0.01$). Based on the model, an eye with the shortest FTBUT (0.5 seconds) would have an estimated 0.6-grade increase in LWE width, compared to the longest FTBUT (60.3 seconds). Asians had an estimated 0.5 greater grade of LWE width than non-Asians; males had an estimated 0.25 greater grade than females; subjects with LIPCOF had an estimated 0.25 greater grade of LWE width than those without.

Lid Wiper Epitheliopathy and Symptoms

Tables 7 and 8 show the separate univariate models examining relationships between LWE and questionnaires in non-contact

lens wearers and contact lens wearers, respectively. For non-contact lens wearers, no questionnaires were significantly associated with LWE length or width in univariate modeling. In contrast, among contact lens wearers, four questionnaires (DEFC, average daily dryness, end-of-day dryness, and frequency of end-of-day dryness) were associated with LWE length. In every questionnaire, all measures except average frequency of discomfort, average daily comfort, and frequency of end-of-day discomfort were associated with LWE width in univariate modeling. In addition, among contact lens wearers, separate univariate models found that LWE length and width were not associated with average daily hours of contact lens wear ($P = 0.18$ and 0.14 , respectively), average daily hours of comfortable contact lens wear ($P = 0.44$ and 0.12 , respectively), and days of contact lens wear per week ($P = 0.71$ and 0.24 , respectively).

With multivariate modeling in contact lens wearers, LWE length was not associated with any questionnaire after factoring in other explanatory variables. However, as shown in Table 9, LWE width was still associated with OSDI ($P = 0.01$), DEFC ($P = 0.01$), SPEED ($P = 0.01$), and all visual analog scales related to dryness ($P = 0.02$ to $P < 0.005$), as well as borderline associated with end-of-day comfort ($P = 0.07$) in contact lens wearers. LWE width was not associated with the CLDEQ-8 ($P = 0.15$) in the multivariate model. Table 9 also lists the coefficient and estimated maximum effect size listed (i.e., comparing the average contact lens wearer in the study who had grade-0 LWE width to one who had grade-3 LWE width) if a significant association was noted. The maximum effect size of LWE width to questionnaires observed was as follows: (1) 2.1 points on SPEED, (2) 5.9 points on OSDI, (3) 0.6 points on DEFC, (4) 15.3 points on average daily dryness, (5) 11.1 points on frequency of dryness, (6) 12.6 points on end-of-day dryness, and (7) 12.3 points on frequency of end-of-day dryness.

DISCUSSION

This large and diverse cross-sectional observational study found that LWE was more prevalent in Asians, contact lens wearers, and younger subjects. It should be noted that the prevalence

TABLE 7. Separate Univariate Models From Non-Contact Lens Wearers Showing the Association Between Grade of LWE Length and Width to Symptoms Reported on Questionnaires

Questionnaire	LWE Length	LWE Width
SPEED score	$P = 0.21$	$P = 0.30$
OSDI score	$P = 0.21$	$P = 0.29$
Dry eye flow chart	$P = 0.10$	$P = 0.67$
Average daily comfort	$P = 0.75$	$P = 0.33$
Frequency of discomfort on average	$P = 0.37$	$P = 0.96$
End-of-day comfort	$P = 0.64$	$P = 0.70$
Frequency of discomfort at end-of-day	$P = 0.62$	$P = 0.89$
Average daily dryness	$P = 0.29$	$P = 0.70$
Frequency of dryness on average	$P = 0.20$	$P = 0.45$
End-of-day dryness	$P = 0.16$	$P = 0.39$
Frequency of dryness at end-of-day	$P = 0.09$	$P = 0.30$

TABLE 8. Separate Univariate Models From Contact Lens Wearers Showing the Association Between Grade of LWE Length and Width to Symptoms Reported on Questionnaires

Questionnaire	LWE Length	LWE Width
SPEED score	$P = 0.17$	$P = 0.01$
OSDI SCORE	$P = 0.17$	$P < 0.005$
Dry eye flow chart	$P = 0.03$	$P < 0.005$
CLDEQ-8	$P = 0.22$	$P = 0.04$
Average daily comfort	$P = 0.58$	$P = 0.08$
Frequency of discomfort on average	$P = 0.69$	$P = 0.35$
End-of-day comfort	$P = 0.15$	$P = 0.04$
Frequency of end-of-day discomfort	$P = 0.24$	$P = 0.06$
Average daily dryness	$P < 0.005$	$P < 0.005$
Frequency of dryness on average	$P = 0.09$	$P = 0.01$
End-of-day dryness	$P = 0.04$	$P < 0.005$
Frequency of end-of-day dryness	$P = 0.02$	$P < 0.005$
Average daily hours of contact lens wear	$P = 0.18$	$P = 0.14$
Average daily hours of comfortable contact lens wear	$P = 0.44$	$P = 0.12$
Days of contact lens per week	$P = 0.71$	$P = 0.24$

Bolded values indicate statistical significance, $P \leq 0.05$.

data might be confounded by the varying composition between demographic groups (i.e., there was a greater proportion of Asians who were contact lens wearers than non-Asians), but similar trends were still seen in multivariate modeling, which accounted for this issue. In the models, a greater severity of LWE length was associated with being Asian, male, and having a decreased FTBUT; LWE width severity was associated with the same factors and also with the presence of LIPCOF. The common thread behind these significant factors is their role in influencing the magnitude of shear stress when the lid wiper interacts with the ocular surface, as the level of shear stress induced is linked with lid anatomy, tear film stability, and contact lens wear.^{5,13}

Lid anatomy likely plays an important role in LWE formation, as it would fundamentally control the level of shear stress that occurs.⁵ A lid anatomy that contributes to greater lid pressure would lead to LWE by increasing shear stress during a blink; in contrast, a lower level of lid pressure would induce less shear stress.^{4,13} It explains why older individuals had a lower rate of LWE, as aging is linked to decreased lid pressure from the decline in muscle tone of the orbicularis oculi and

involutional changes to collagen, elastin, and glycosaminoglycan in the eyelid.^{37,49,50} It would explain why females were found to have a lower severity in LWE, as Francis et al.⁵¹ have found that females have lower lid tension than males. Finally, it could explain why Asians were nearly twice as likely to present with LWE than non-Asians and have a greater severity in LWE length and width, as the distinctive ocular anatomy in Asians, having greater herniation of orbital fat and smaller palpebral aperture size, may collectively contribute to greater lid pressure.^{21,52} Increased shear stress in Asians has been linked to their greater corneal epithelial permeability, corneal staining, and likelihood for developing inflammatory adverse events during extended contact lens wear than for non-Asians.^{21,40–42}

An additional reason for why Asians had a higher prevalence of LWE may be linked to their reported greater tear film instability, compared to non-Asians, which has been attributed to the difference in meibum composition.^{30,40,42,53} Even though an association between poor tear film stability and LWE was observed, it would require a nearly 60-second decrease in FTBUT to obtain a 0.6- and 0.8-grade increase in LWE length and width, respectively. Owing to the relatively small effect sizes of LWE by FTBUT, the use of artificial tears would likely not reduce the severity of LWE in a clinically meaningful way, even with a moderate to significant improvement in tear film stability (e.g., 5–15 seconds). This is supported by the study of Guthrie et al.,⁵⁴ where the application of a lipid-based emulsion four times a day for a month improved LWE by only half a grade, which would offer a marginal benefit to someone with grade-3 LWE. Treatment of severe LWE would likely necessitate the targeting of a different disease pathway in LWE, such as the use of topical mucin secretagogues to increase mucin production in the ocular surface.^{55,56}

Although greater tear film instability is noted with contact lens wear, it only plays a minor role in why a higher prevalence of LWE was observed in contact lens wearers; this conjecture is supported by the small effect size of LWE by FTBUT observed in our statistical model. Instead, it is the higher coefficient of friction (CoF) in contact lens compared to an ocular surface without contact lens that may be a major contributor for the difference in LWE.^{57,58} CoF is defined as the relationship of friction between two interfacing surfaces, with contact lens CoF determined by material, as well as deposits that develop

TABLE 9. Separate Multivariate Models Examining the Relationship Between LWE Width and Questionnaires in Contact Lens Wearers*

Questionnaire	P Value of LWE Width as an Explanatory Variable	Coefficient of LWE Width	Estimated Maximum Effect
SPEED score	0.01	0.71	2.1
OSDI score	0.01	1.97	5.9
Dry eye flow chart	0.01	0.20	0.6
CLDEQ-8	0.15		
End-of-day comfort	0.07		
Average daily dryness	<0.005	5.1	15.3
Frequency of dryness on average	0.01	3.7	11.1
End-of-day dryness	0.02	4.2	12.6
Frequency of end-of-day dryness	0.02	4.1	12.3

Bolded values indicate statistical significance, $P \leq 0.05$.

* Coefficient and estimated maximum effect size are listed if LWE width was found to be a significant explanatory variable.

during wear.¹³ The importance of contact lens CoF is highlighted by studies that suggest that its increase may be associated with increased contact lens discomfort and corneal staining.^{13,57,58} It has also been found that LWE can develop shortly after individuals start wearing contact lenses.⁴³ It is therefore conceivable that a regular and smooth surface (either contact lens or cornea) that comes in contact with the lid wiper is a prerequisite for a healthy lid wiper. From our anecdotal clinical observations, most of our patients with significant conjunctival chalasis or with surgical sutures on the ocular surface experience LWE. The presence of LWE disappears or its severity subsides after removal of redundant conjunctival tissues or surgical sutures, suggesting the importance of a regular ocular surface to promote smooth and lubricious contact between the ocular surface and the lid wiper.

It is interesting to note that the association between LWE and symptoms was only observed in contact lens wearers. This may be due to the fundamental difference between the ocular surface with versus without contact lenses.^{59,60} Even with advances in modern contact lens surfaces, it is impossible to fully mimic innate ocular surface characteristics, which have a thicker tear film and a mucin-enriched layer on the cornea.⁵⁹⁻⁶² To understand if the influence of LWE width on contact lens-related symptoms is clinically significant, it is important to assess how each grade of change in LWE width affects symptoms and whether it constitutes a meaningful change on the questionnaires. On the OSDI, a 3-grade increase in LWE width is needed to obtain a minimal clinically important difference for mild to moderate dry eye.⁶³ For the visual analog scales for dryness, a 2- to 3-grade increase in LWE width is needed to obtain a barely noticeable difference.⁶⁴ This argues that although LWE can increase symptoms in contact lens wearers, it would require the presence of moderate to severe LWE width for it to be considered clinically meaningful enough to change. Therefore, switching the contact lens of a symptomatic contact lens wearer from one with a higher CoF to one with a lower CoF may only be of clinical value if moderate to severe LWE width is observed.

One limitation of this study was assessing LWE only on the upper lid. This choice was made because LWE on the lower lid may be primarily due to increased tear osmolarity⁶⁵ and not shear stress, and because the movement observed in the lower lid is predominantly lateral (as opposed to vertical movements in the upper lid).^{13,43} Owing to these uncertainties, only the upper LWE was examined to focus on the influence of a shear stress-driven phenomenon. Another study limitation was that lissamine green was the only dye used to stain for LWE, while previous studies have used a twin-dye method (a combination of lissamine green, fluorescein, and rose bengal).^{3-5,13} However, recent studies on LWE predominantly use lissamine green by itself, and the twin-dye method does not appear to provide any diagnostic benefits.¹³ It is possible that some of the LWE in contact lens wearers may have resolved during the 24 hours the subjects were required to discontinue contact lens wear. However, owing to cellular changes observed in LWE,⁶⁶ we suspected that at most, there would only be a minor change in the lid wiper epithelium within that period. From our clinical experience, we hypothesized that discontinuation of contact lens wear for 24 hours would offer the best balance of preserving ocular surface changes induced by soft contact lens wear (e.g., LWE) while still obtaining baseline tear film characteristics.

The results from this study indicate that although significant associations were noted for certain ocular signs, patient characteristics, and questionnaires to LWE, they were, for the most part, not as clinically significant as previous studies have found.^{3,5,43} The difference may be attributed to the selection

and sample size of the study cohort. The published studies that strongly support LWE typically have used a fairly narrow inclusion criterion for symptomatic and asymptomatic subjects or have smaller sample sizes.^{3,5,43} The findings from this study, which were based on a large and diverse study cohort, are likely more representative of the clinical significance of LWE in the general population.

This study reinforces the theory that LWE is likely a result of increased shear stress that is mediated by lid anatomy, tear film stability, and contact lens wear. The prevalence of LWE is high, but it may not be clinically significant owing to the small effect sizes of LWE induced by these aforementioned factors. Our data also suggest that LWE is primarily significant among symptomatic contact lens wearers with moderate to severe LWE width. In those cases, interventions such as switching to a lens material with a lower CoF may improve symptomatology.

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